The claimed methods and pharmaceutical compositions relate to oligonucleotides that are defined as hybridizing to strategic sites of the bcl-2 sequence such as a translation initiation, splice donor or splice acceptor sequence of SEQ ID NO:19; or hybridizing to at least one of the first six codons of the reading frame of SEQ ID NO:19, or to the 5'-cap region of SEQ ID NO:19. In accordance with the claimed invention, the specification provides that the anticode oligomers can be administered to patients to inhibit the proliferation of tumor cells (see, the instant specification at page 14, line 16, to page 15, line 6 and page 15, line 25, to page 16, line 33).

The anticode oligomers of the claimed invention hybridize to specific strategic sites of the bcl-2 gene. The specification provides that "[b]locking translation at such strategic sites prevents formation of the functional bcl-2 gene product." (p. 12 of the instant specification). These "strategic sites" are clearly defined by the specification and by the claims. *See, e.g.*, the instant specification describes targeting the first six codons of bcl-2 in the treatment of lymphoma cell (p. 46, lines 4-6 of the instant specification); other preferred examples of regions of the bcl-2 gene to be targeted include the translation initiation site, splice donor and splice acceptor sequence of SEQ ID NO:19 (Table 1, p. 13 of the instant specification); and the translation initiation site or the 5'-cap region of SEQ ID NO:19 (p. 33 of the instant specification). The specification provides evidence of the efficacy of utilizing the anticode oligomers that hybridize to the strategic sites of the bcl-2 gene. Examples 2-18 of the specification provide data from both *in vitro* and cell based assays which demonstrate the efficacy of the claimed oligonucleotides in reducing the level of bcl-2 and in killing cancer cells, in particular lymphoma cells (pp. 21-57 of the specification). The data generated from the cell based assays demonstrates the ability of the antisense oligomers of the invention to permeate across the membrane of eukaryotic cells, hybridize to the bcl-2 mRNA in its native form and effectively inhibit the growth of a variety of tumor cells. The specific "antisense

effect" of the antisense oligomers is confirmed by the complete inability of the control sense oligomers to affect cell growth.

Further, the efficacy of the claimed invention as demonstrated in cell based assays has been confirmed by the post-filing art. In particular, it has been shown that the pharmaceutical compounds and methods of the instant invention reduced tumor mass and led to an improvement in symptoms for cancer patients. (Webb et al., 1997, Lancet 349:1137-41). Moreover, Delihas has described numerous clinical trials that are underway on various types of cancer using the compositions and methods of the instant invention. (Delihas, 2001, Curr. Drug Targets 2:167-80). These studies confirm that the antisense oligomers of the invention can be used to treat cancer patients when used in accordance with the teaching of the specification. These studies further confirm that one skilled in the art would be able to follow the teaching of the specification and use the cell based data provided therein to treat cancer patients with the claimed oligomers without undue experimentation. In order to satisfy the enablement requirement, a considerable amount of experimentation is permissible and not considered undue, so long as it is merely routine. *See In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicant reasserts that the claimed invention is fully enabled, and should not be precluded by the necessity for some experimentation involving routine screening and testing. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). Applicant respectfully submits that the expectation of success for identifying useful bcl-2 antisense oligonucleotides of 10 to 40 bases in length <u>targeted against the strategic sites of SEQ ID NO:19</u> is no less than testing an array of hundreds (or thousands) of hybridomas to identify <u>one</u> useful monoclonal antibody, and thus the claimed invention is clearly within the purview of the skilled artisan. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). In fact, the instant technology often permits the identification of several antisense sequences involving screening of only a few dozen candidate sequences.

According to the M.P.E.P., "the courts have repeatedly held, all that is required is a *reasonable* correlation between the activity and the asserted use." § 2107.03 (I) (emphasis added). Applicant asserts that the instant specification provides objective scientific data demonstrating antisense activity that *reasonably* correlates to *in vivo* applications. In fact, such assays are routinely used in the art of antisense technology to identify and test antisense oligonucleotides for human treatment. Using the methods of the instant invention, the post-filing art confirms this correlation. Thus, the teachings of the instant specification, in combination with the state of the art as of the filing date, fully enable the claimed invention.

In summary, the claims are drawn to the treatment of cancer in humans, and the claimed oligonucleotides now target "strategic sites" of SEQ ID NO:19, which are fully described by the specification. These strategic sites are identified by the specification and the post-filing art as effective targets to decrease the level of bcl-2 and kill human cancer cells. Since the art at the time of filing provides, *inter alia*, methods of administration, dosing and toxicity assays, and the post-art documents human treatment using pharmaceutical compositions comprising antisense oligonucleotides of the instant invention, the invention is fully enabled under 35 U.S.C. § 112. As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing remarks into the file of the above-identified application. Applicant believes that each ground for rejection or objection has been overcome or obviated, and that all of the pending claims are in condition for allowance. Applicants respectfully request consideration of the pending claims and withdrawal of the rejection. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosures